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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

June 20, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane - Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under § 701 and other applicable sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 371] and 21 CFR 10.30 to request the Commissioner of Food and Drugs to establish a regulation to define labeling requirements for dietary supplements containing St. John's wort (*hypericum perforatum*).

A. Action Requested

The Consumer Healthcare Products Association (CHPA)[1] asks that FDA issue a regulation to require a label statement on dietary supplements containing St. John's wort (*hypericum perforatum*) pertaining to potential prescription drug interactions.

CHPA requests that FDA amend its drug information advisory, information sheets and guidances from the Center for Drug Evaluation and Research and available in written or electronic form to include St. John's wort (*hypericum perforatum*) as a dietary constituent that may interact with drugs known to be metabolized by the cytochrome P450 pathway.

CHPA requests that the compliance date for a final regulation on this matter be one year from the publication of the final rule in the *Federal Register* based on date of manufacture.

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[1] CHPA is the 119-year-old trade organization representing dietary supplements and nonprescription drugs, including over 200 members across the manufacturing, distributing, supply, research testing, and advertising sectors of the self-care industry.

B. Statement of Grounds

1. Background

On February 10, 2000 FDA issued a Public Health Advisory[2] on the risk of interactions between St. John's wort and indinavir and other drugs. This advisory was based on the results from a study conducted by the National Institutes of Health (NIH) showing a significant drug-dietary supplement interaction between St. John's wort (hypericum perforatum) and indinavir, a protease inhibitor used to treat HIV infection. As noted by FDA in the advisory, "concomitant administration of St. John's wort and indinavir substantially decreased indinavir plasma concentrations, potentially due to induction of the cytochrome P450 metabolic pathway." Piscitelli et al. reported that "St. John's wort reduced the area under the curve of the HIV-1 protease inhibitor indinavir by a mean of 57% (SD 19) and decreased the extrapolated 8-h indinavir trough by 81% (16) in healthy volunteers ..." and concluded that "a reduction in indinavir exposure of this magnitude could lead to the development of drug resistance and treatment failure" (Reference 10).

Based on these results, FDA projected that St John's wort "may significantly decrease blood concentrations of all of the currently marketed HIV protease inhibitors (PIs) and possibly other drugs (to varying degrees) that are similarly metabolized, including the nonnucleoside reverse transcriptase inhibitors (NNRTIs)" and concluded that "concomitant use of St John's wort with PIs or NNRTIs is not recommended because this may result in suboptimal antiretroviral drug concentrations, leading to loss of virologic response and development of resistance or class cross-resistance." FDA concluded in its Health Professional Letter of February 10, 2000 (Reference 3):

> "Based on this study and reports in the medical literature, St. John's wort appears to be an inducer of an important metabolic pathway, cytochrome P450. As many prescription drugs used to treat conditions such as heart disease, depression, seizures, certain cancers or to prevent conditions such as transplant rejection or pregnancy (oral contraceptives) are metabolized via this pathway, health care providers should alert patients about these

[2] Food and Drug Administration: Risk of Drug Interactions with St. John's wort and Indinavir and Other Drugs. Letter to Health Professionals from Murray M. Lumpkin, M.D., February 10, 2000.

potential drug interactions to prevent loss of therapeutic effect of any drug metabolized via the cytochrome P450 pathway."

Other published studies provide support to FDA's conclusion that the findings of the Piscitelli study may apply more broadly to a number of prescription drugs. For example:

- In the same issue of Lancet that carried the Piscitelli report, Ruschitzka et al. (Reference 12) described two cases of acute heart transplant rejection due to metabolic interaction of St John's wort (300 mg t.i.d., containing 900 μg hypericin) and cyclosporine. Decreased cyclosporine plasma concentrations and acute rejection (International Society of Heart and Lung Transplantation, ISHT grading 3A and 2, respectively) were reported on admission for two heart transplant patients. The investigators observed, "after stopping treatment with St. John's wort, plasma ciclosporin [sic] remained within the therapeutic range with no further episodes of rejection."

- Nebel et al. (Reference 9) reported a potential metabolic interaction between St. John's wort and theophylline. The patient was on multiple drug therapy, including furosemide, potassium, morphine, zolpidem, valproic acid, ibuprofen, amitryptyline, albuterol, prednisone, zafirlukast, and inhaled triamcinolone acetonide, as well as being a smoker. However, the authors reported that, since John's wort (300 mg b.i.d. standardized to 0.3% hypericin) was "the only other agent added since problems arose with her theophylline concentrations, the patient decided on her own to discontinue the St. John's wort," resulting in an approximate doubling of her theophylline plasma level from 9.2 μg/mL to 19.6 μg/mL and a subsequent downward adjustment of her theophylline dosage.

- Lantz et al. reported a series of five cases of clinically diagnosed central serotonergic syndrome among elderly patients who combined prescription antidepressants with St. John's wort. (Note: reference not available from local library resource center. See Reference 16 for abstract.)

- Barbenel et al. reported a manic episode experienced by a patient who developed depression following bilateral orchidectomy for cryptorchidism and continued St.

John's wort self-treatment while taking a serotonin re-uptake inhibitor. (Note: reference not available from local library resource center. See Reference 17 for abstract.)

- Several studies suggest multiple possible mechanisms of action for interactions between St. John's wort and prescription drugs.
  - Since the publication of FDA's advisory on St. John's wort, Moore et al. (Reference 8) demonstrated that "St. John's wort activates the orphan nuclear receptor PXR and consequently induces the expression of CYP3A4, a monooxygenase that plays a central role in the metabolism of most drugs. Moore et al. also concluded, "Our finding that hyperforin, an abundant, lipophilic component of St. John's wort, is a high-affinity PXR ligand provides evidence that a single constituent of hypericum extracts contributes to both the therapeutic effects and the side effects of this herb."
  - While at least one study (Reference 7) suggests St. John's wort at recommended dosages over short durations of use may not interact with prescription drugs through the CYP2D6 or CYP3A4 components of the cytochrome pathway, other studies, such as Roby et al. (Reference 11), support the conclusions of Moore et al., finding that a 14-day treatment with St. John's wort (300 mg t.i.d. standardized to 0.3% hypericin) in young volunteers (age 18-25 years) "resulted in significant increases in the urinary 6-β-hydroxycortisol/cortisol ratio ...[suggesting] that St. John's wort is an inducer of CYP3A4."
  - Johne et al. (Reference 5) investigated the interaction between hypericum extract LI160 and digoxin in a single-blind, placebo-controlled parallel study in healthy volunteers, finding, after the achievement of steady state for digoxin, a 10-day treatment regimen with hypericum extract resulted in a decrease of digoxin AUC(0-24) by 25% (day 15, 17.2 +/- 4.0 μg h/L and 12.9+/-2.3 μg h/L; P = .0035), as well as a reduction in trough concentrations and C_{max} of 33% (P = .0023) and 26% (P = .0095), respectively. Johne et al.

suggested that the mechanism of digoxin-St. John's wort interaction may be induction of the P-glycoprotein drug transporter.

- Other studies suggest a possible effect of St. John's wort on extracellular concentrations of central monoamines and glutamine (References 1, 6 and 13), leading various authors of review articles and compendial sources to advise caution when using, or caution against use of, St. John's Wort when taking prescription antidepressants (References 2, 4, and 14).

In summary, the Piscitelli report in conjunction with the added published information cited above provide a weight of evidence that supports use of a drug-herbal interaction statement on the labels of dietary supplements containing St. John's wort.

FDA has a long-standing policy that label statements must be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer."[3] This policy has stood up very well as a framework for working through public health issues relating to the labeling of self-care products. It is a three-part standard, with credible scientific documentation as the first hurdle. Without adequate scientific documentation there is no need to determine whether the effect under scrutiny has clinical significance, let alone importance to the consumer use situation. Thus, based on this policy construct and given the weight of the evidence from the published findings presented above, CHPA members who market dietary supplements containing St. John's wort have recently adopted a voluntary labeling program (see next section).

2. CHPA's Voluntary St. John's Wort Labeling Program

a. Voluntary Label Statement

In the interest of consumers and patients who may choose to use St. John's wort, CHPA members who market St. John's wort-containing dietary supplements have adopted a voluntary labeling program that places the following statement on dietary supplements

[3] E.g.: Final Rule Regarding Label Warning for Pregnant or Nursing Women; Delegations of Authority and Organization. 47 *Federal Register* 54750-58 (12/3/82).

containing St. John's wort: "If you are taking a prescription drug, ask a health professional." (Reference 15)

This statement (or its reasonably substantial equivalent; see 2.b.), when included in the labeling of dietary supplement products defined by the voluntary program, is intended to be prominent and conspicuous and may appear in one of a number of alternative forms which convey essentially the same information intended by the label statement cited above (see below re: Alternative Statements).

b. Alternate Statements:

As with other CHPA voluntary label statements (e.g., CHPA's voluntary pregnancy/nursing labeling program), this proposed statement may be used in reasonably substantially equivalent wording, such as:

- ask *(*or, *consult;* or, *contact)*[4] a *(*or, *your)* doctor *(*or, *health professional;* or, *health care practitioner)* if you are taking a prescription medicine (or, *drug)*;
- ask *(*or, *consult;* or, *contact)* a *(*or, *your)* doctor *(*or, *health professional,* or *doctor or other health professional;* or, *health care practitioner)* before using this product if you are taking a prescription medicine *(*or, *product)*;
- if you are taking a prescription medicine *(*or, *product)*, ask (or, *consult*) a *(*or, *your)* doctor *(*or, *health professional,* or *doctor or other health professional;* or, *health care practitioner)*";
- if you are taking *(*or, *currently taking)* a prescription medicine *(*or, *product)*, ask *(*or, *consult;* or, *contact)* a *(*or, *your)* doctor *(*or, *health professional,* or *doctor or other health professional;* or, *health care practitioner)* before using *(or, before using this product)*;
- Or other reasonably substantially equivalent statements.

c. Combination of the Voluntary St. John's Wort Label Statement with Other Similar Voluntary Label Statements:

The voluntary St. John's wort label statement may be combined with other voluntary labeling statements, such as the CHPA pregnancy/nursing label statement,

[4] Words in italics represent examples of reasonably equivalent wording, and are not to be considered inclusive of all possible reasonably equivalent statements.

provided the combined language creates a logical construct (e.g., "If you are taking a prescription medicine, or, if you are pregnant or nursing a baby, ask a doctor").

d. Implementation Date of the CHPA Voluntary St. John's wort Labeling Program:

The implementation date for labeling the CHPA voluntary St. John's wort labeling program is the next label printing, but not later than April 2, 2001.

C. Environmental Impact

CHPA does not believe under 21 CFR 25.30 that the requested actions individually or cumulatively have a significant effect on the human environment, and that therefore neither an environmental assessment nor an environmental impact statement is required.

D. Lack of Economic Impact and Compliance Date

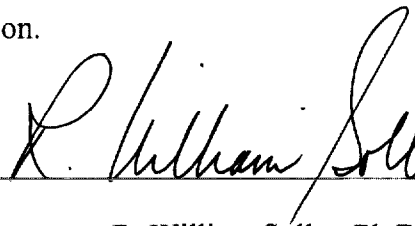
Although FDA specifies that specific economic information is to be submitted only when requested by the Commissioner following review of the petition, CHPA points out that the majority of CHPA members already comply with the CHPA voluntary St. John's wort labeling program.

In addition, the CHPA voluntary program has a compliance date of April 2, 2001, for its dietary supplement member companies. The compliance date is approximately one year after the formal adoption of the voluntary program, which was on March 22, 2000. The approximate one-year compliance date is consistent with the one-year compliance date stipulated in other final rules.

Action requested: CHPA requests that the compliance date for a final regulation on the St. John's wort labeling program be one year from the publication of the final rule in the *Federal Register* based on date of manufacture.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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Attachment: References (1-17)

WS/jkq:Dietsupp/VoluntaryLabelingProgramsCitizenpetitionSt.John'sWlabeling.6/19/00

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